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Pathology

Etiology of fibrous dysplasia and McCune-Albright syndrome

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Abstract. In this paper, the etiology of monostotic fibrous dyplasia and McCune-Albright syndrome is explained. Both monostotic fibrous dysplasia and McCune-Albright syndrome are sporadically occurring disorders in which a mutation in the GNAS1 gene occurs postzygotically in a somatic cell. All cells descended from the mutated cell can manifest features of McCune-Albright syndrome or fibrous dysplasia. Cells descended from non-mutated cells develop into normal tissues. Thus, the clinical pattern is variable in distribution and appearance. More generalized *vs* more localized expression depend on (a) how small or how large the cell mass is during embryogenesis when the mutation occurs and (b) where in the cell mass the mutation occurs. Topics discussed include G proteins and their receptors, cycling of stimulatory G protein between active and inactive forms, and specific mutations in GNAS1. We also discuss four possibilities: (a) Are there masked mutations? (b) Are there effects of imprinting? (c) Are there non-classical mutations? and (d) Is fibrous dysplasia a neoplasm?

Key words: fibrous dysplasia; pituitary adenoma; McCune-Albright syndrome; GNAS1 gene; G protein; somatic mosaicism; neoplasia.

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Monostotic fibrous dysplasia is a well-known bone disorder of great interest to surgeons and pathologists. The etiology is now known. Activating mutations in the gene that encodes the α subunit of stimulatory G protein ($G_s\alpha$) cause monostotic fibrous dysplasia, polyostotic fibrous dysplasia, pituitary adenoma, and McCune-Albright syndrome. To understand the etiology, G proteins, G protein-coupled receptors, cycling of stimulatory G protein ($G_s\alpha$) between its active and inactive forms, and the concept of somatic mosaicism need to be explained. Terminology used in this paper is summarized in Table 1.

G proteins, particularly $G_s\alpha$

G proteins (guanine nucleotide proteins) are a family of molecules composed of three subunits designated α, β, and γ. The function and specificity of each G protein is determined by the α subunit, which is unique for each type. The β and γ subunits tend to be more homogeneous. In this paper, we shall be concerned with stimulatory G protein ($G_s\alpha$) which activates adenylyl cyclase which, in turn, catalyzes the formation of cAMP (3′,5′-cyclic adenosine monophosphate) from ATP (adenosine triphosphate). The gene for $G_s\alpha$ is GNAS1 (guanine nucleotide-binding protein, α-stimulating activity polypeptide 1); its chromosome map location is 20q13.2[15].

Like all G proteins, the inactive form of $G_s\alpha$ contains bound GDP (guanosine diphosphate). A GPCR (G protein-coupled receptor) facilitates the exchange of bound GTP (guanosine triphosphate) for GDP producing the active form[30,31].

G protein-coupled receptors

G protein-coupled receptors link the binding of an extracellular ligand, such as a growth factor or hormone, to the activation of the associated G protein and intracellular signal generation. The GPCR family has seven hydrophobic membrane-spanning domains, an extracellular amino-terminal region, and an intracellular carboxy-terminal region. The intracellular loop between the fifth and sixth membrane-spanning domains together with the intracellular carboxy-terminal segment are important for G protein interactions[30,31].

Cycling stimulatory G protein ($G_s\alpha$) between its active and inactive forms

Cycling of stimulatory G protein ($G_s\alpha$) between its active and inactive forms is

Table 1. Terminology

Abbreviations	Definitions
ATP	Adenosine triphosphate
cAMP	3′,5′-cyclic adenosine monophosphate
CS	Catalytic subunit of PKA
DAG	Diacylglycerol
$G_{\beta\gamma}$	$\beta\gamma$ subunit of G protein
GDP	Guanosine diphosphate
GNAS1	Guanine nucleotide-binding protein, α-stimulating activity polypeptide 1
GPCR	G protein-coupled receptor
$G_s\alpha$	α subunit of G protein
GTP	Guanosine triphosphate
GTPase	Guanosine triphosphatase
IP_3	Inositol trisphosphate
MAS	McCune-Albright syndrome
MFD	Monostotic fibrous dysplasia
PA	Pituitary adenoma
PFD	Polyostotic fibrous dysplasia
PIP_2	Phosphatidylinositol bisphosphate
PKC	Protein kinase C
PKA	Protein kinase A or cAMP-dependent protein kinase
PLC	Phospholipase C
RS	Regulatory subunits of PKA
STK	Serine/threonine kinase

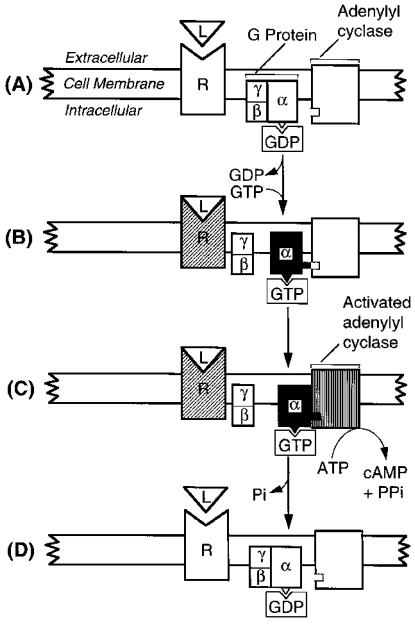

Fig. 1. Activation of adenylyl cyclase following ligand binding to G protein-coupled receptor. (A) G protein composed of α, β, and γ subunits. This is the inactive form. L=Ligand. R=Receptor. GDP=Guanosine diphosphate. (B) Ligand (L) binding produces conformational change in receptor (R) and guanosine diphosphate (GDP) is replaced by guanosine triphosphate (GTP), resulting in dissociation of the α subunit. (C) Binding of α subunit to adenylyl cyclase activates 3′,5′-cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). (D) Hydrolysis of GTP to GDP by GTPase, causing dissociation of the α subunit from adenylyl cyclase and binding to the β and γ subunits, the inactive form. Ligand binding causes repetition of the cycle.

Table 2. Mutations in the GNAS1 Gene

Disorder	Exon	Nucleotide change	Amino acid substitution
McCune-Albright syndrome	8	C→T	Arg201Cys
	8	G→A	Arg201His
Polyostotic fibrous dysplasia	8	C→T	Arg201Cys
Monostotic fibrous dysplasia	8	C→T	Arg201Cys
	8	G→A	Arg201His
Panostotic fibrous dysplasia	8	C→A	Arg201Ser
Isolated pituitary adenoma	8	C→T	Arg201Cys
	8	G→A	Arg201His
	8	C→A	Arg201Ser
	9	A→G	Gln227Arg
	9	G→T	Gln227His

Based on Weinstein et al., 1991[34], Schwindinger et al., 1992[25], Shenker et al., 1993[29], 1994[28], 1995[27], Candeliere et al., 1995[4], Landis et al., 1989[14], Malchoff et al., 1994[16], Williamson et al., 1995[35], Candeliere et al., 1997[3].

shown in Fig. 1. The inactive $G_s\alpha$ is shown in (A) and (D). Ligand-binding (B) produces a conformational change in the receptor and GDP is replaced by GTP, which results in dissociation of the α subunit. Binding of the active form of the α subunit to adenylyl cyclase (C) activates this enzyme, resulting in the formation of cAMP from ATP. Hydrolysis of GTP to GDP is catalyzed within seconds by the intrinsic GTPase (guanosine triphosphatase) activity of $G_s\alpha$ causing dissociation of the α subunit from adenylyl cyclase and binding to the β and γ subunits, resulting in the inactive form (D). Ligand-binding will cause repetition of the cycle[31].

Mutations in GNAS1

Mutations in GNAS1 have been associated with different disorders. Gain-of-function mutations have been found in McCune-Albright syndrome (MAS), polyostotic fibrous dysplasia (PFD), monostotic fibrous dysplasia (MFD), and pituitary adenoma (PA). Loss-of-function mutations have been found in endocrine disorders characterized by hormone resistance, such as type 1a pseudohypoparathyroidism, hereditary glucocorticoid deficiency, and nephrogenic diabetes insipidus[30].

Bone marrow contains hematopoietic tissue and skeletal progenitor cells of the marrow spaces[19]. GNAS1 mutations in MAS cause hyperfunction of (1) skeletal progenitor cells from the marrow spaces producing abnormal osteoblasts[2,19], (2) melanocytes[25], and (3) endocrine cells[9]. The same abnormal osteoblasts are also found in PFD and MFD. To date, no mutations have been reported in Jaffe-Lichtenstein syndrome characterized by polyostotic fibrous dysplasia and café-au-lait spots without endocrine disturbances. Since this syndrome is part of the same clinical spectrum, it can be assumed that a GNAS1 mutation is causative.

How activating GNAS1 mutations affect the cycling of $G_s\alpha$ between its active and inactive forms is shown in Fig. 2. One of two specific mutations can be demonstrated in these disorders (Table 2): C→T, resulting in Arg201Cys, or G→A, resulting in Arg201His.

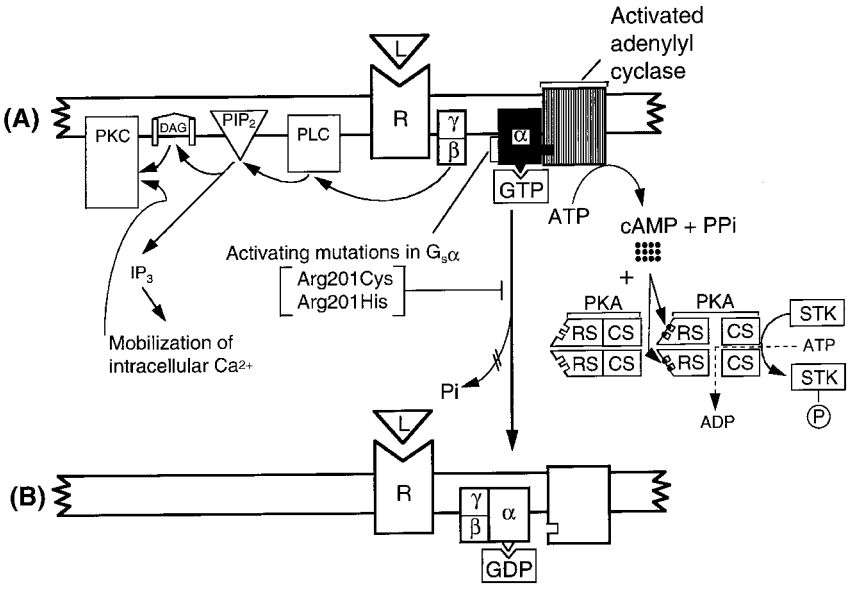

Fig. 2. Activating mutations (Arg201Cys or Arg201His) in the gene encoding the α subunit of stimulatory G protein ($G_s\alpha$). (A) Ligand-independent persistent activation of $G_s\alpha$. There is inappropriate stimulation of adenylyl cyclase. The mutations are located adjacent to the γ-phosphate of GTP, thus interfering with hydrolysis of GTP by GTPase to GDP. (B) Therefore, the α subunit ($G_s\alpha$) cannot dissociate from adenylyl cyclase and bind to the $\beta\gamma$ subunit ($G_{\beta\gamma}$). Two downstream pathways are shown in A. The PKC pathway (protein kinase C pathway) is shown on the left. The PKA pathway (protein kinase A or cAMP-dependent protein kinase pathway) is shown on the right. Both pathways are present with normal functioning as well as with mutations. However, to keep Figures 1 and 2 as simple as possible, these pathways are omitted except in 2A. The PKC and PKA pathways are specifically shown in 2A because the mutations interfere with hydrolysis of GTP to GDP, resulting in continued stimulation of the α subunit ($G_s\alpha$) and continued dissociation of the $\beta\gamma$ subunit ($G_{\beta\gamma}$). The dissociated $\beta\gamma$ subunit overactivates the PKC pathway. PLC (phospholipase C) cleaves PIP_2 (phosphatidylinositol bisphosphate) into two intracellular messengers: DAG (diacylglycerol) and IP_3 (inositol trisphosphate). The latter triggers the release of sequestered calcium ions (Ca^{2+}) which together with DAG activate PKC. Because the α subunit ($G_s\alpha$) cannot dissociate from adenylyl cyclase, cAMP is overproduced which, in turn, overactivates the PKA pathway. PKA is composed of two regulatory subunits (RS) that have binding sites for cAMP, and two catalytic subunits (CS) that, when dissociated, phosphorylate serine/threonine kinases (STK).

Activation is maintained in a ligand-independent manner (Fig. 2A), producing inappropriate stimulation of adenylyl cyclase. Mutations are located near the site which interacts with the γ-phosphate of GTP, thus interfering with hydrolysis of GTP to GDP. Because $G_s\alpha$ cannot dissociate from adenylyl cyclase and bind to $G_{\beta\gamma}$, adenylyl cyclase remains active, producing increased cAMP activity which results in the pathology of MAS, PFD, MFD, and PA.

Two downstream pathways: protein kinase A and protein kinase C

Activation of $G_s\alpha$ linked receptors opens multiple downstream pathways. Two important pathways are the protein kinase A or cAMP-dependent protein kinase pathway (PKA pathway) and the protein kinase C pathway (PKC pathway) (Fig. 2A). These pathways were not considered earlier to keep the molecular biology from being overly complicated. For the same reason, these pathways were omitted in Figure 1. They must be considered with activating GNAS1 mutations, however, because continued activation of the α subunit ($G_s\alpha$) results in (1) increased cAMP which overactivates the PKA pathway and (2) continued dissociation of the $\beta\gamma$ subunit ($G_{\beta\gamma}$) which may synergistically stimulate adenylyl cyclase and stimulates some isoforms of PLC[5] (Fig. 2A). PKA can produce many effects depending on the cell type and the particular proteins PKA phosphorylates. In the PKC pathway, once PKC is activated, it activates the MAP kinase pathway. These pathways produce various types of cellular response and play a fundamental role in controlling cell growth.

Because the α subunit ($G_s\alpha$) cannot dissociate from adenylyl cyclase, cAMP is overproduced which, in turn, overactivates the PKA pathway (Fig. 2A). PKA is composed of two regulatory subunits (RS) that have binding sites for cAMP, and two catalytic subunits (CS) that, when dissociated, phosphorylate serine/threonine kinases (STK).

The dissociated $\beta\gamma$ subunit ($G_{\beta\gamma}$) overactivates the PKC pathway[5]. Phospholipase C (PLC) cleaves phosphatidylinositol bisphosphate (PIP_2) into two intracellular messengers: diacylglycerol (DAG) and inositol trisphosphate (IP_3). The latter triggers the release of sequestered calcium ions (Ca^{2+}) which, together with DAG, activate PKC.

McCune-Albright syndrome, fibrous dysplasia, and somatic mosaicism

McCune-Albright syndrome (MAS) is characterized by polyostotic fibrous dysplasia, café-au-lait spots, and multiple endocrinopathies, including sexual precocity, pituitary adenoma, and hyperthyroidism. Many other abnormalities are known to occur and these have been reviewed and discussed by Shenker et al[29]. In 1986, Happle[10], noting that MAS occurred sporadically, set forth the intriguing hypothesis that the disorder was caused by somatic mosaicism, lethal in the non-mosaic state. Sporadic occurrence and variability of expression in MAS are compatible with Happle's hypothesis.

With somatic mosaicism, a mutation occurs postzygotically in a somatic cell rather than in a germ cell. All cells descended from the mutated cell can manifest MAS features. Cells descended from non-mutated cells develop into normal tissues. Thus, the clinical pattern is mosaic in distribution and variable in appearance. Severe versus mild manifestations and more generalized versus more localized expression depend on (a) how small or how large the cell mass is during embryogenesis when the mutation occurs and (b) where in the cell mass the mutation occurs.

The same two GNAS1 mutations found in MAS also occur in polyostotic fibrous dysplasia (PFD), monostotic fibrous dysplasia (MFD), and isolated pituitary adenoma (PA) of the growth hormone secreting type[a], less commonly of the ACTH secreting

[a] If the epiphyses are closed, patients can develop acromegaly.

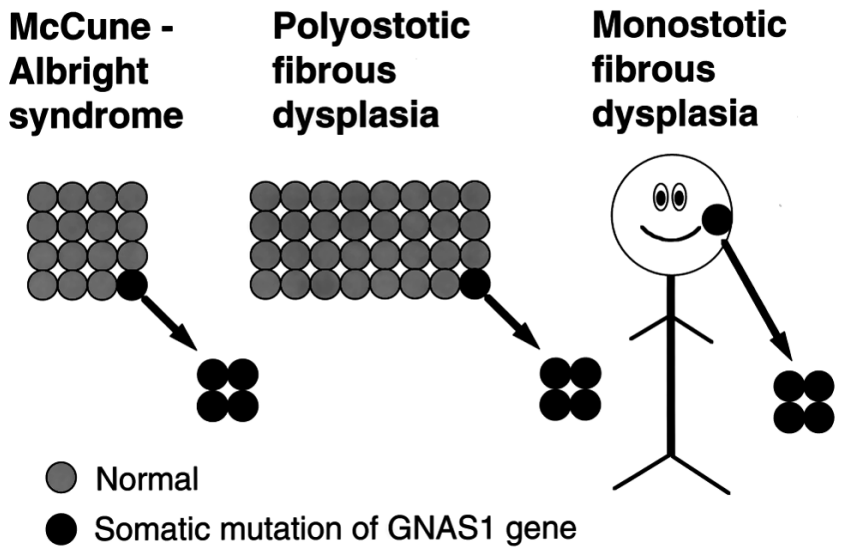

Fig. 3. How mutations cause McCune-Albright syndrome, polyostotic fibrous dysplasia, and monostotic fibrous dysplasia depend on when during embryonic development or during postnatal life the mutation occurs. Somatic mutation in a small cell mass is likely to result in McCune-Albright syndrome. Mutation in a larger cell mass may result in polyostotic fibrous dysplasia. A mutation in postnatal life, during infancy, childhood, or adult life may result in monostotic fibrous dysplasia.

type[1,3,9,11,14,16,27–29,34,35] (Table 2). How these mutations cause these disorders separately depends on when during embryonic development or during postnatal life the mutation occurs (Fig. 3). Somatic mutation in a small cell mass is likely to result in MAS. Mutation in a larger cell mass may result in PFD. A mutation in postnatal life, during infancy, childhood, or adult life may result in MFD (Fig. 3) or in PA, depending on the anatomic location of the mutation. All of these disorders are components of MAS.

Fibrous dysplasia: other possibilities

Are there masked mutations?

One possibility may be that somatic mutations may not become manifest *ab initio*, but survive in masked form to become active at a later time. For example, a mutation for monostotic fibrous dysplasia may occur during fetal life, but not become manifest until 25 years of age.

That such a possibility is worth considering is borne out by the study of *Drosophila* mutations by Rutherford & Lindquist[23]. They suggested that the *Drosophila* genome contains masked mutations protected by "heat shock proteins" that stabilize the mutant proteins and keep them functioning properly. When the organism is stressed, "heat shock proteins" no longer protect the mutant proteins which then become unmasked, altering physical traits in harmful ways.

Are there effects of imprinting?

In genomic imprinting, modifications in the genetic material occur depending on whether genetic information is maternally or paternally derived. If the paternal allele is imprinted (inactive), the maternal allele is active. In contrast, if the maternal allele is imprinted (inactive), the paternal allele is active. Imprinted genes can be on autosomes, and the effects can be tissue-specific or more generalized. For example, genes at 11p15.5, such as IGF2 and $p57^{KIP2}$, among other genes, have differential maternal and paternal effects[7].

Pseudohypoparathyroidism is also caused by mutations in GNAS1, but inactivating ones that reduce the expression and function of $G_s\alpha$. Some patients with pseudohypoparathyroidism have resistance to multiple hormones, while others have resistance to only some hormones. The 1a type of pseudohypoparathroidism is almost always inherited maternally, suggesting that GNAS1 is an imprinted gene. Hayward et al.[12] were able to demonstrate differential methylation between maternal and paternal alleles. Yu et al.[38] generated mice with a null allele in Gnas (the mouse homologue of human GNAS1). Maternal ($Gnas^{m-/p+}$) and paternal ($Gnas^{m+/p-}$) heterozygotes for the null allele were shown to have distinct phenotypes. Resistance to parathyroid hormone was present in $Gnas^{m-/p+}$ but not in $Gnas^{m+/p-}$ mice. Thus, variable hormone resistance appears to be explained by Gnas imprinting in mice. Similar imprinting in human GNAS1 may explain differences in hormone resistance and the variable phenotypes observed in pseudohypoparathyroidism. Juppner et al.[13] showed that the gene defect in type 1b pseudohypoparathyroidism was paternally imprinted and was therefore maternally inherited in the same manner as the type 1a form.

GNAS1 is on an autosome (20q13.2)[15] and, since imprinting takes place early in development, the gene may be imprinted before a somatic mutation takes place. Possible imprinting effects of an activating mutation in GNAS1 for monostotic fibrous dysplasia, polyostotic fibrous dysplasia, pituitary adenoma, and McCune-Albright syndrome remain unknown. We suggest that mutated cells in these disorders be studied to determine if any differences exist between maternally and paternally expressed cells.

Are there non-classical mutations?

A minority of cases may be caused by non-classical mutations (Table 2). For example, Gln227Arg and Gln227His may be found in some instances of isolated pituitary adenoma. An Arg201Ser mutation has been reported in a case of panostotic fibrous dysplasia. Whether these mutations or possibly some downstream mutations are found in a minority of cases or in rare cases of the spectrum of disorders listed in Table 2 remains to be determined. Studies of other genetic disorders have sometimes shown that a small percentage of patients have mutations other than the classical ones known to cause the disorders. For example, mutations in the gene patched are found commonly in basal cell carcinoma and in medulloblastoma. However, mutations downstream of patched have been recorded in a few instances[6].

Is fibrous dysplasia a neoplasm?

Traditionally, fibrous dysplasia has been considered a bone disorder. However, it

is well-known that, in a few instances, lesions in fibrous dysplasia behave more aggressively than in most cases. The same activating mutation that causes fibrous dysplasia also causes pituitary adenoma which is a neoplasm. The mutation may be found in isolated pituitary adenoma and in McCune-Albright syndrome which is often associated with pituitary adenoma.

Candeliere et al.[4] found high levels of c-fos proto-oncogene expression in cells populating the bone marrow spaces in eight patients with fibrous dysplasia. In contrast, very low levels of c-fos expression were detected in other bone disorders such as vitamin D-resistant rickets and osteogenesis imperfecta, suggesting that increased expression of c-fos may be specific for fibrous dysplasia. If so, activating mutations in GNAS1, which cause fibrous dysplasia, may increase c-fos expression by increased adenylyl cyclase activity.

Candeliere et al.[4] noted that the cells populating the bone marrow spaces were fibroblasts. Riminucci et al.[19] and Bianco et al.[2] found that the GNAS1 mutated cells occupying the marrow spaces were skeletal progenitor cells that produced abnormal osteoblasts. The fibroblasts of Candeliere et al.[4] may, in fact, be skeletal progenitor cells, but not so named because the research on this topic was not published at the time of the Candeliere et al. study. The high levels of c-fos expression and the mutated GNAS1-induced increase in adenylyl cyclase may thus be occurring in the same cell.

In studies of transgenic mice, overexpression of c-fos results in bone lesions that closely resemble fibrous dysplasia[21] and osteosarcomas develop in some cases[22]. In studies of human osteosarcomas, c-fos expression is increased[36]. Osteosarcomas are known to develop in about 4% of patients with McCune-Albright syndrome and in about 0.5% of patients with fibrous dysplasia[37].

Osteosarcoma has been shown to be caused by ionizing radiation in some cases[8]. Post-irradiation osteosarcoma has also been observed in a number of cases of fibrous dysplasia[24,32]. The combination of a GNAS1 mutation, increased c-fos expression, and radiation exposure in a few cases suggests multistep carcinogenesis of osteosarcoma, which could account for the low frequency of tumors in cases of fibrous dysplasia.

In summary, fibrous dysplasia manifests as single or multiple bone tumors that progressively enlarge. Lesions are composed of islands of immature woven bone within a mass of fibroblast-like cells. They essentially consist of unencapsulated clonal proliferations of fibroblast-like osteoprogenitor cells with an activating mutation of GNAS1, which demonstrate constitutively high expression of the proto-oncogene c-fos. The osteoprogenitor cells, or derived cell lines, have an increased rate of proliferation and display markers of early osteoblastic differentiation but undergo abnormal maturation and fail to express normal levels of late osteoblastic markers[17,19]. These findings describe a lesion best categorized as a benign unencapsulated neoplasm.

Are there different types of fibrous dysplasia?

Riminucci et al.[20] have suggested site-specific patterns of histopathology in fibrous dysplasia. They identified three patterns: Chinese writing type, associated with the axial and apendicular skeleton; sclerotic/Pagetoid type, associated with the cranial bones; and sclerotic/hypercellular type, associated with the maxilla and the mandible. Fifteen specimens from the axial and apendicular skeleton were studied, but only three specimens each were studied from the cranial bones and the jaws[20]. Thus, the sample size for these latter anatomic sites is small.

Our own experience is different. We have seen numerous examples of jaw lesions with C-shaped or Chinese character-shaped bony trabeculae. The distribution of discontinous bony trabeculae in a "remarkably ordered, often parallel, pattern" suggested by Riminucci et al.[20] has only been observed by us occasionally. Our experience is also borne out by authorities in oral and maxillofacial pathology[18,26].

Various radiographic appearances are found with fibrous dysplasia of the jaws. Radiolucent lesions may be unilocular or multilocular. A mottled radiolucent/radiopaque pattern may also be observed in some cases which can be described as Pagetoid[18,26]. Waldron & Giansanti[33], in a study of 65 cases of fibrous dysplasia of the jaws, noted that jaw lesions mature with time and may show lamellar bone. Thus, the mature form of fibrous dysplasia has a Pagetoid radiographic appearance similar to what Riminucci et al.[20] have described. However, it is important to note that many cases of fibrous dysplasia of the jaws do not have either the histologic or radiographic appearance described by Riminucci et al.[20].

To the extent that there may be histopathologic diversity of bone lesions in fibrous dysplasia, they may be explained by the different structural features of various bones, as suggested by Riminucci et al.[20]. For example, the sclerotic component of the craniofacial lesions may reflect a higher ratio of compact to cancellous bone than that found in the long bones and vertebral column.

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